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EXAMINER	
WILSON, MICHAEL C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/485,943	FRIEDMAN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124,132-137,139-143,145-150,155-159 and 163-174* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124, 132-137, 139-143, 145-150, 155-159 and 163-174* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-123, 125-131, 138, 144, 151-154, 160-162 and 175 have been canceled. Claims 124, 132-137, 139-143, 145-150, 155-159 and 163-174 remain pending and under consideration in the instant office action.

Applicant's arguments filed 10-31-07 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Please separate arguments regarding new matter and written description. While arguments may be repeated, each new matter rejection should be addressed separately.

Claim Objections

Claims 136, 137, 150 and 174 should begin "The method of claim...". Applicants argue the claims as written are proper. Applicants' argument is not persuasive. Dependent claims should clearly refer back to the method of claim X, not a method of claim X.

Claims 145-149 and 155-159 are objected to because they do not clearly set forth that the mammal exhibits a decrease in body weight or that the therapeutic effect is decrease in body weight. Applicants argue they may claim a scope that is within applicants' disclosure. Applicants' argument is not persuasive. The claims require administering a "therapeutically effective amount" of adenovirus encoding OB without clearly setting forth the therapeutic effect. The specification does not contemplate

administering a "therapeutic effective amount" of adenovirus encoding OB without obtaining a therapeutic effect, i.e. a decrease in body weight. This issue is also addressed in the enablement rejection regarding the breadth of treating any mammal.

Claim Rejections - 35 USC § 112

Enablement

Claims 124, 132-137, 139-143, 145-150, 155-159 and 163-174 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Breadth of the claims

The claims are drawn towards a method of modifying the weight of a mammal using a vector encoding an ob protein under conditions that provide for expression of the ob protein in vivo. The ob proteins in the claims include SEQ ID NO: 2 (mouse ob), SEQ ID NO: 4 (human ob) and variations thereof (see claims for details regarding the variations). The preamble of the claim 124 requires "modifying the body weight of a mammal". The body of the claim requires administering the vector to a mammal "wherein the vector is administered in a therapeutically effective amount such that the mammal exhibits a decrease in body weight". Therefore, administration of a vector encoding ob must decrease body weight to have an enabled use according to the specification.

State of the art regarding the ob gene/protein

The obese (ob) gene product is equivalent to the leptin gene product (Tartaglia, 1995, Cell, Vol. 83, pages 1263-1271; see abstract, line 1; see the instant application on pg 5, lines 5-16).

Ob/ob mice with a homozygous disruption in the ob gene were known to be obese (pg 3, lines 3-6).

At the time of filing, it was unknown whether obese ob/ob mice correlated to obese humans with a gene mutation. Since the time of filing, Clayton (Arch. Dis. Child, 1998, Vol. 78, 278-284) taught that 5% of humans with obesity have an ob concentration lower than expected (pg 282, col. 1, line 20).

The specification states: "Because of the myriad factors that seem to impact body weight, it has not been possible to predict which factors and, more particularly, which homeostatic mechanisms is actually primarily determinative. Nonetheless, the apparent connections between the ob gene and the extent and characteristics of obesity have prompted the further investigation and elucidation that is reflected by the present application. It is the identification of the sequence of the gene and corresponding peptide materials, to which the present invention following below directs itself." (pg 4, lines 14-20).

Thus, it was unpredictable whether ob/ob mice correlated to any obese human or to a gene disruption that occurred in humans.

At the time of filing, the art did not teach what tissue expressed the ob protein. Nor did the art teach in what tissues the ob protein mediated an effect. Since the time

of filing, Tartaglia (cited above, Dec. 29, 1995, Cell, Vol. 83, pages 1263-1271) confirmed that up to 1995, the tissue in which the ob protein mediated an effect remained unknown (pg 1263, col. 2, line 2).

Thus, the tissue target required to express ob or to mediate a decrease in body weight in a mammal was unknown at the time of filing.

Since the time of filing, Fletcher (Nov. 15, 1995, Blood, Vol. 86, page 241a) taught decreasing the body weight of an obese mouse having a homozygous mutation in the ob gene by administering bone marrow from an autologous mouse transduced with a retroviral vector encoding ob to the bone marrow of the recipient mouse (page 241a, line 12).

Morsy (1998, Proc. Natl. Acad. Sci., USA, Vol. 95, pages 7866-7871) taught that 60% weight loss can be obtained for 6-7 weeks following administration of a leptin-encoded adenoviral vector (pg 7870, col. 1, line 13); however, analysis revealed eventual loss of the vector DNA 4 and 8 weeks following administration of the vector (pg 7870, col. 2, line 5).

Unpredictability of gene therapy

At the time of filing and since, the combination of vector, promoter, dosage, target tissue, level of expression and route of administration required to target the desired tissue so that a therapeutic would occur was unpredictable.

Feldman (Fundamental & Clinical Pharmacology, 1995, Vol. 9, pg 8-16) suggested treating restenosis using a vector encoding a protein. Feldman discussed experiments in which the vector administered to the arterial wall during angioplasty

allowed low levels of protein expression in cells of the arterial wall. Feldman taught that obtaining a therapeutic effect was prevented by low numbers of cells expressing a transgene, transfection efficiency, target specificity, and sustained expression (pg 12, "Arterial gene therapy"). None of the experiments described by Feldman resulted in a therapeutic effect.

Miller (Feb. 1995, FASEB J., Vol. 9, pg 190-199) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (pg 198, col. 1). Miller did not obtain a therapeutic effect using gene delivery.

Crystal (Oct. 20, 1995, Science, Vol. 270, pg 404-410) also reviewed various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (pg 409). Crystal did not obtain a therapeutic effect using gene delivery.

Verma (Sept. 1997, Nature, Vol. 389, pg 239-242) reviewed vectors for use in gene therapy and discussed problems associated with adenoviral vectors and indicates a resolution to vector targeting has not been achieved in the art (see entire article). Verma also taught appropriate regulatory elements may improve expression, but it is

unpredictable what regulatory elements target what tissues (pg 240, sentence bridging col. 2-3). Verma did not obtain a therapeutic effect using gene delivery.

Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69) indicated that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviewed new techniques under experimentation in the art that show promise but stated that such techniques were even less efficient than viral gene delivery that failed to work (see pg 65, 1st ¶ under "Conclusion"). Deonarain did not obtain a therapeutic effect using gene delivery.

Ross (Sept. 1996, Human Gene Therapy, Vol. 7, pg 1781-1790) stated a major technical impediment to gene transfer is the lack of ideal gene delivery systems including vectors, promoters and modes of delivery (pg 1782, col. 2, 1st full ¶). The ability to use gene therapy to obtain a therapeutic effect in a patient was unpredictable (Ross, pg 1789, col. 1, 1st ¶). Ross did not obtain a therapeutic effect using gene delivery.

Therefore, it was unpredictable what combination of vector, promoter, dosage, cells, level of expression and route of administration would provide a therapeutic effect using gene delivery.

Teachings of the specification

Pg 5, line 10 teaches the "leptin" protein is absent in plasma of ob/ob mice. The specification does not teach the leptin protein is absent in obese humans.

The specification on pg 73-83 describes protein-based therapy for obesity. On pg 74, lines 18-27, applicants describe administering the ob protein by intravenous, intraarterial, intraperitoneal, intramuscular or subcutaneous routs of administration. Pg 83, line 3, through pg 84, line 24, describes administering the ob gene using a vector to decrease body weight of a mammal. The description of nucleic acid-based therapies on pg 83 does not include a description of the conditions required to obtain expression of the protein or the route of administration. The disclosure on pg 74 is limited to protein administration and does not include vector administration. One of skill in the art would not read the description of routes of administration for proteins on pg 74 as applying to the nucleic acid-based therapy on pg 83 because they are addressed individually and separately (see separate sections for "Polypeptide-based therapeutic treatment" and "Nucleic acid-based therapeutic treatments" on pg 73 and 83). The specification does not reasonably imply that the routes of delivery for proteins discussed in the "polypeptide-based therapeutic treatment" should be used for "nucleic acid-based therapeutic treatments."

Pg 83, line 4, teaches the ob gene can be "introduced into human fat cells to develop gene therapy for obesity." The specification does not teach how to target vectors to adipocytes using *in vivo* gene delivery. The specification does not teach what cells mediate the function of the ob protein so that one of skill could target a vector encoding ob to those cells.

Pg 83, lines 3-26, lists viral vectors for delivering the ob gene. For example, defective viral vectors allow "for administration to cells in a specific, localized area,

without concern that the vector can infect other cells. Thus, adipose tissue can be specifically targeted." Such vectors include HSV, papillomavirus, EBV adenovirus, AAV and retrovirus. Pg 84, lines 1-17, describes introducing a vector by lipofection. Pg 84, lines 18-24 describe administering the vector as naked DNA plasmid. The specification does not teach the specific combination of vector, promoter, route of administration and dosage required to obtain ob expression in a mammal such that a decrease in body weight is obtained.

Pg 90 begins the examples section, which include gene mapping of the mouse and human ob gene, cloning of the mouse and human ob gene, preparing the ob protein, preparing antibodies to the ob protein and recombinant expression of the ob protein in bacteria.

Pg 118, line 23, pg 12, line 10, through pg 125, line 2, and pg 125, Table 1, teach administering the ob protein to three strains of ob/ob mice. The ob/ob mice lost weight.

Pg 129, Example 9, and pg 126, Example 10, describe increased expression of ob in adipocytes as compared to other tissues. Since the time of filing, it has been confirmed that ob was expressed exclusively in adipose tissue (Clayton, cited above, pg 282, col. 1, line 3).

Pg 144, line 22, and pg 120, lines 1-25, describe the ob serum levels in mice and humans.

Pg 147, Example 11, teaches the human ob protein is active in ob/ob mice.

The specification teaches delivering ob protein to treat obesity on pg 73-74 but does not provide adequate guidance for one of skill to obtain the same serum level ob using gene delivery.

Rejection

Overall, the specification does not overcome the unpredictability in the art by teaching the specific combination of vector, promoter, dosage and route of administration required to target ob expression to fat cells or how to express ob protein so it will target the tissue that mediates a reduction in body weight.

In view of the art recognized unpredictability in gene therapy and the mere list of possible vectors provided by applicants on pg 83 and 84 without teaching the route of administration or dosage, those of skill in the art would be left to perform an undue amount of experimentation to determine the specific combination of vector, promoter, route of administration and dosage required to reduce body weight in a mammal. In particular, the specification does not provide adequate guidance for those of skill to determine the target tissue for decreasing the body weight of a mammal using leptin gene therapy, the specific route of administration required to transfect the target tissue, or the amount of leptin expression in the target tissue required to reduce body weight.

The specification does not disclose any assays that would reveal the tissues in which OB was expressed or mediated its effects. Applicants do not point to a reference that first discloses the tissues in which OB was expressed or mediated its effects and confirms that the methods of doing so were well known at the time of filing the instant application. Tartaglia (cited above) confirmed that in December 1995, the tissue in

which the ob protein mediated an effect remained unknown (pg 1263, col. 2, line 2). Applicants have not adequately taught how to target OB expression to its native expressing tissue or to target OB to the tissue in which it mediates its effects. Determining the tissue to target is only the first of a number of hurdles applicants have left for those of skill to perform the method claimed.

Since the time of filing, Fletcher (cited above) decreased the body weight of an obese mouse having a homozygous mutation in the ob gene by administering bone marrow from an autologous mouse transduced with a retroviral vector encoding ob to the bone marrow of the recipient mouse (page 241a, line 12). In view of the unpredictability in the art of gene therapy, the specific combination of retrovirus, transduced bone marrow cells and bone marrow administration is essential to the invention. Applicants do not enable the claimed invention because applicants do not describe the specific combination of retrovirus, transduced bone marrow cells and bone marrow administration, which is essential to reduce body weight as taught by Fletcher.

Morsy (cited above) obtained weight loss by administering 1-2 x 10^{11} particles of helper adenoviral vector encoding leptin via the tail vein of ob/ob mice (pg 7869, col. 2; pg 7870, Fig. 4B, Fig. 5B, col. 1). In view of the unpredictability in the art of gene therapy, the specific combination of adenovirus, tail vein injection and the dosage of 1-2 x 10^{11} particles is essential to the invention. Given the state of the art regarding the ob gene/protein taken with the teachings in the specification, one of skill would not have expected intravenous administration to cause ob expression in adipocytes as contemplated by applicants as being the source of ob expression. Nor would one of

skill have known that intravenous administration would cause ob expression capable of targeting cells that mediate a therapeutic effect. Applicants do not enable the claimed invention because the specification does not describe the specific combination of adenovirus, tail vein injection and the dosage of 1-2 x 10^{11} particles, which is essential to reduce body weight as taught by Morsy.

Muzzin of record (PNAS, Dec. 1996, Vol. 93, pg 14804-14808) obtained weight loss of ob/ob mice by administering 3 x 10^9 particle forming units of helper adenoviral vector encoding leptin via the tail vein (pg 14805, ¶ bridging col. 1-2 and col. 2, 1st full ¶). In view of the unpredictability in the art of gene therapy, the specific combination of adenovirus, tail vein injection and the dosage of 3 x 10^9 pfu is essential to the invention. One of skill would not have expected that intravenous administration would cause expression in adipocytes as contemplated by applicants as the source of the majority of ob expression. Nor would one of skill have expected that intravenous administration would cause ob expression capable of targeting cells capable of mediating a decrease in body weight. Applicants do not enable the claimed invention because the specification does not describe the specific combination of adenovirus, tail vein injection and the dosage of 3 x 10^9 pfu, which is essential to reduce body weight as taught by Muzzin.

Chen (1996), Murphy (1997), Buettner (2000), Dube (2002) and Larcher (2001) all successfully reduced body weight using vectors encoding leptin. The references were not available at the time of filing and cannot be relied upon for enablement. In fact, the references teach factors that were not disclosed in the specification as

originally filed. Chen, for example, used 60 bp of leptin cDNA 5' untranslated and 76 bp of 3' untranslated as well as the translated region. The leptin coding region was placed in an adenoviral vector under the control of the CMV promoter. The resulting adenovirus was administered via a tube into the carotid artery in the dosage of $1x10^{12}$ PFU. The teachings of Chen, Murphy, etc. are not in the specification as originally filed. The methods of Chen, Murphy, etc. are not readily to those of skill in the art at the time of filing from applicants' disclosure as originally filed.

Furthermore, the claims encompass decreasing the body weight of any mammal using a vector encoding an ob protein. However, the specification and the art since the time of filing are limited to treating mammals with an ob deficiency with the ob protein. The specification does not correlate the obese mammals having a defective ob gene to any other obese mammals or any other obesity related gene defect. The specification does not provide an enabled use for decreasing the body weight of a wild-type mammal (having a normal weight). Therefore, it would require one of skill undue experimentation to determine how to use the vector encoding ob to treat obesity in any mammal as broadly claimed other than those with a defective ob gene.

Certain claims encompass using any analog of an ob protein that modulates body weight. The specification defines analogs as ob proteins that agonize or antagonize the function of the ob protein. In other words, the claims encompass administering a vector encoding a protein that antagonizes the function of the ob protein and causes a weight increase. The specification does not teach any ob proteins that antagonize the function of ob. The specification does not teach how to use the ob

protein analogs to increase weight. Without such guidance it would require one of skill in the art undue experimentation to determine antagonistic analogs of the ob protein or how to use vectors encoding ob proteins capable of increasing body weight.

The specification does not enable using a vector encoding an ob protein having any substitution as broadly encompassed by 134, 135, 142, 143, 148, 149, 158, 159 and 165-173. Salvador (Exp. Opin. Pharmacotherapy, 2001, Vol. 2, No. 10, pg 1615-1622) taught leptin is 167 amino acids in length and has the body weight control functions confined to amino acids residues 106-140. The specification teaches the conservative and non-conservative substitutions between the mouse and human leptin proteins in Fig. 4. It is noted that the specification does not define what they consider "conservative" and "non-conservative" substitutions. The specification does not teach the functional region of the leptin protein or that any substitution as broadly claimed will allow the leptin protein produced to control body weight. Without such guidance it would have required one of skill undue experimentation to determine which amino acids could be substituted without altering the active site of leptin or to determine which amino acids could be substituted without altering the structure of the active site or the function of leptin.

Response to applicants' arguments

Applicants argue targeting OB to a particular tissue using gene therapy is not an issue claimed or required in applicants' invention. Applicants point to pg 25, line 24, through pg 26, line 7, which teaches OB is a circulating factor that is secreted by cells that express it. Applicants' argument is not persuasive. Pg 83, lines 18-19, suggests

using gene therapy to introduce the ob gene "into human fat cells to develop gene therapy for obesity". The specification specifically discloses targeting the OB gene to fat cells. In fact, that is the only means of gene therapy contemplated in the specification as originally filed. Intravenous administration of the leptin protein is discussed in the specification, but intravenous administration of the ob gene cannot reasonably be implied from the specification. The specification does not suggest performing gene therapy such that systemic expression of OB occurs, does not teach the cells that secrete OB and does not teach how to perform gene therapy such that OB is secreted systemically.

Applicants argue Fletcher, Morsy and Muzzin demonstrate that selection of an adenovirus encoding leptin, the dosage, route of administration and target tissue are not critical to decrease body weight as claimed. Applicants' argument is not persuasive. Fletcher, Morsy and Muzzin were not available at the time of filing and cannot be used to establish the state of the art. The specific teachings of Fletcher, Morsy and Muzzin, administering transduced bone marrow cells systemically or systemic administration of a vector, are not readily apparent from the specification originally filed. Furthermore, Fletcher, Morsy and Muzzin are limited to systemic administration of a vector encoding OB; however, the claims encompass any route of administration. Finally, assuming arguendo that Fletcher, Morsy and Muzzin established the combination of elements using gene therapy was not critical to decrease body weight, Fletcher, Morsy and Muzzin did so only after the effective filing date of this application; those of skill in the art would have not have believed the combination of elements required to decrease body

weight was crucial. The teachings in the specification do not provide adequate guidance to overcome the art established unpredictability of gene therapy by teaching the specific combination of elements required to decrease body weight using gene therapy.

Applicants argue Chen, Murphy, Buettner, Dube and Larcher confirm the limitations claimed were enabled at the time of filing. Applicants argue the essential elements described by Chen, Murphy, Buettner, Dube and Larcher were taught in applicants' specification. Applicants' argument is not persuasive. The specification does not teach the essential elements described by the references. Chen, for example, used 60 bp of leptin cDNA 5' untranslated and 76 bp of 3' untranslated as well as the translated region. The leptin coding region was placed in an adenoviral vector under the control of the CMV promoter. The resulting adenovirus was administered via a tube into the carotid artery in the dosage of $1x10^{12}$ PFU. None of these elements described by Chen are described by applicants or readily apparent from the specification. The specific elements required to decrease body weight using gene therapy are essential to the invention in view of the general unpredictable state of the art of gene therapy. Furthermore, pg 83, lines 18-19, is limited to introducing the ob gene "into human fat cells to develop gene therapy for obesity"; the only means of gene therapy contemplated in the specification is into fat cells, not into the carotid artery as described by Chen. Intravenous administration of the leptin protein is discussed in the specification, but intravenous administration of the ob gene cannot reasonably be implied from the specification. The teachings of Chen, Murphy, etc. are not in the

specification as originally filed and are not readily to those of skill in the art at the time of filing from applicants' disclosure as originally filed.

Applicants argue Feldman, Miller, Crystal, Verma, Deonarain and Ross (used to establish the unpredictability of gene therapy in general) are irrelevant because they do not teach gene therapy using the OB gene. Applicants' argument is not persuasive. Those of ordinary skill in the art at the time of filing thought the combination of vector, route of administration, dosage and target tissue required to obtain the desired effect using various genes used for therapy was unpredictable. The specification does no more than suggest using gene therapy to introduce the ob gene "into human fat cells to develop gene therapy for obesity" (pg 83, lines 18-19) and list a host of possible vectors, promoters and transfection reagents and methods. Accordingly, the unpredictability of gene therapy in general bears weight when analyzing the claims. The mere suggestion of a host of possible combinations of gene therapy elements was not adequate guidance at the time of filing to indicate OB gene therapy was any different. In particular, the specification does not reasonably imply systemic delivery of the OB gene, which was shown after the time of filing to decrease body weight. The unpredictability of gene therapy in general must be given weight at the time of filing in view of the specification that merely lists possible gene therapy elements, lacks a suggestion of systemic delivery of the OB gene and lacks examples of gene therapy.

Applicants argue the specification teaches a list of vectors, promoters, transfection reagents and methods on pg 54, lines 1-19, pg 83, line 21, through pg 85, line 10, and ascertaining weight loss on pg 72, lines 5, through pg 73, line 6. Therefore,

applicants conclude the specification enables determining the combination of elements required to decrease body weight using gene therapy. Applicants' argument is not persuasive. The specification does no more than suggest using gene therapy to introduce the ob gene "into human fat cells to develop gene therapy for obesity" (pg 83, lines 18-19) and list a host of possible vectors, promoters and transfection reagents and methods. The specification does not reasonably imply systemic delivery of the OB gene, which was shown after the time of filing to decrease body weight. The specification does not provide any examples of gene therapy. Accordingly, the specification does not provide adequate guidance to overcome the art established unpredictability of gene therapy and enable those of skill to determine the specific combination of elements required to decrease body weight using gene therapy.

Applicants argue pg 125, lines 26-27, indicates the claims need not be limited to treating mammals with an OB deficiency. Applicants point to pg 5, lines 10-14, pg 125, line 26, through pg 126, line 2 and pg 126, line 2 and Table 1. Applicants' argument is not persuasive. The specification does not disclose an enabled use for decreasing the body weight of wild-type mice using the OB protein or gene. The purpose of the invention is to treat obese mammals having a leptin deficiency.

Applicants argue analogs that agonize or antagonize the function of the ob protein are not encompassed by the claims because they are limited to methods of decreasing body weight. Applicants' argument is not persuasive. The claims encompass using analogs that agonize or antagonize the function of the ob protein to decrease body weight, which is not enabled. Furthermore, claims 145-149 and 155-159

do not clearly set forth that the mammal exhibits a decrease in body weight or that the therapeutic effect is decrease in body weight. It cannot be determined how a leptin analog that antagonizes the weight loss function of the ob protein can be used in the method claimed. Therefore, the rejection regarding the claims that encompass using any analog of an ob protein that modulates body weight is proper.

Applicants argue the claims do not require conservative and non-conservative substitutions; therefore, the specification need not define conservative and non-conservative substitutions. Applicants' argument is not persuasive. Claims 134, 135, 142, 143, 148, 149, 158, 159 and 165-173 encompass a vector encoding an ob protein having conservative or non-conservative substitution. Salvador (2001) of record, taught leptin is 167 amino acids in length and has the body weight control functions confined to amino acids residues 106-140. The functional region of the leptin protein was not known at the time of filing and not taught in the specification. Not any substitution as broadly claimed will allow the leptin protein produced to control body weight. Therefore, the rejection regarding the breadth of substitutions is proper.

Applicants argue the specification contemplates introducing the OB gene by means other than "into human fat cells to develop gene therapy for obesity" (pg 83, lines 18-19). Applicants argue the statement on pg 83 does not negate other modes of delivery. Applicants' argument is not persuasive. No other means of delivering the OB gene is taught in the specification. Intravenous administration of the leptin protein is discussed in the specification, but intravenous administration of the ob gene cannot reasonably be implied from the specification. The section of "nucleic acid-based

therapeutic treatments" on pg 83-84 is limited to targeting fat cells and is separate and distinguished from protein based therapies discussed elsewhere in the specification. It is not readily apparent that applicants contemplated administering a leptin gene intravenously from the leptin protein therapy protocols because they are discussed distinctly and separately in the specification.

New Matter

Claims 124, 132-137, 139-143, 145-150, 155-159 and 163-174 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "operatively linked to a promoter" in claims 124, 132-135, 139-143, 145-149, 155-159 and 163-173 remains new matter. Pg 51, lines 8-16, describes coding sequences "under the control" of transcriptional and translational control sequences. The scope of such sequences is not the same as "operatively linked to a promoter." Furthermore, the expression control sequences described on pg 52, line 7, through pg 53, line 15, are limited to in vitro expression of ob because they are part of the description of unicellular hosts for producing the protein *in vitro* (see pg 52, line 2; "yeast" on line 19; pg 53, lines 9-15; pg 54, lines 7-9). The scope of "promoter" is narrower in scope than "transcriptional and translation control sequences" as originally contemplated in the specification as originally filed and is new matter. Applicants'

arguments under "Status of the claims" regarding "operatively linked to a promoter" are noted.

Applicants argue pg 51, line 1, pg 52, line 8, supports the phrase. Applicants' argument is not persuasive. The citation is limited to coding sequences "under the control" of transcriptional and translational control sequences; the scope of such sequences is not the same as "operatively linked to a promoter" as claimed. Applicants argue the phrase "operatively linked to a promoter" is within the genus described in the specification. Applicants' argument is not persuasive. The species was not contemplated and is not readily apparent in the specification as originally filed. Applicants argue the meaning of the phrase was well known in the art. Applicants' argument is not persuasive because that particular species was not contemplated in the specification as originally filed.

The concept of an OB protein comprising "amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53... ...166 is substituted with another amino acid" in claims 134, 142, 148 and 158 remains new matter. Fig. 4 describes specific conservative substitutions of the amino acids of the mouse and human ob polypeptide using asterisks at amino acids 53, 92, 98, 118, 121, 122, 126-128, 132, 139, 159 and 166 and specific non-conservative substitutions using a dash at amino acids 71, 85, 89, 110, 129, 157 and 163. The specification is limited to specific amino acid difference at the positions claimed and does not suggest substituting amino acids at the positions claimed with any amino acid

as broadly claimed; therefore, substituting amino acids at the positions claimed with any amino acid is broader than the substitutions originally contemplated and is new matter.

Applicants' arguments have been considered but the analysis section fails to address the specifics of the rejection. In particular, pg 26 concludes applicants described multiple OB proteins capable of decreasing body weight and having 0-17% amino acid sequence variability. Applicants' argument is not persuasive. The analysis fails to point out where the specification supports the concept of an OB protein comprising "amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53... ...166 is substituted with another amino acid" in claims 134, 142, 148 and 158. "Little substantial variation of amino acids between species within the genus of OB proteins" as suggested by applicants in the arguments at the end of pg 26 of the response is inadequate to support the specific substitutions in claims 134, 142, 148 and 158. The species are not readily apparent from the genus.

Applicants argue the substitutions claimed are readily apparent from Fig. 4. Applicants argue a representative number of species encompassed by the claims are described explicitly or implicitly (pg 27 of the response). Applicants' arguments are not persuasive. The species claimed are not disclosed in the specification either explicitly or implicitly. Please address each new matter rejection separately and point to explicit or implicit support for each. If support is implicit, please provide a reasoned statement why support is implicit. Fig. 4 fails to support the substitutions claimed because it is limited to specific substitutions. It notes conservative and non-conservative amino acid

differences when comparing human and mouse OB proteins but not the substitutions claimed. In particular, Fig. 4 does not contemplate substituting the amino acids claimed with any amino acid as broadly claimed.

The concept of an OB protein comprising "amino acids 22-166 of SEQ ID NO: 6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with another amino acid" in claim 135, 143, 149, 159 remains new matter. The specification does not suggest substituting the amino acids in the Gln deleted mutants in Fig. 5 and 6, specifically with any amino acid as broadly claimed. It is not readily apparent that the conservative and non-conservative differences between the mouse and human protein in Fig. 4 are places for substituting amino acids in the Gln mutants in Fig. 5 and 6, specifically with any amino acid as broadly claimed.

Applicants argue the "analysis above yields the same result with respect to the claimed genus Gln deleted proteins. It is readily apparent that simply subtracting "1" from each amino acid position number as recited in claims 134, 142, 148 and 158 that comes after position 49, which corresponds to the Gln that is disclosed to be deleted in the ob polypeptides depicted in each of Figs, 5 and 6, yields the recited positions for substitutions which correspond to the position recited in claims 134, 142, 148 and 158." Applicants' argument is not persuasive. Fig. 4 is limited to comparing the differences between the human and mouse OB protein and does not contemplate substituting the amino acids marked with a * or – with any amino acid as broadly claimed. Figure 5 is limited to mouse ob lacking glutamine at position 49 (pg 12, lines 24-26). Fig. 6 is

limited to human ob lacking glutamine at position 49 (pg 12, lines 24-26). Apparently applicants are arguing the substitutions in claims 135, 143, 149 and 159 are limited to the OB proteins of Fig. 5 and 6; however, the claims 135, 143, 149 and 159 are not limited to the OB proteins of Fig. 5 and 6. Nor is it readily apparent applicants contemplated making the substitutions Fig. 4 in the proteins of Fig. 5 and 6. Subtracting "1" from the amino acids of the protein in Fig. 4 to make similar substitutions in the proteins of Fig. 5 and 6 is not readily apparent. The specification does not suggest substituting the amino acids in the Gln deleted mutants in Fig. 5 and 6 with any amino acid as broadly claimed.

The substitution in claim 166, g) regarding positions 118-166 remains new matter. Applicants point to Fig. 4 taken with pg 35, lines 11-12, which described the helix potential of the disulfide loop of amino acids 117-167, pg 34, lines 14-19, which states disulfide bonded loop analogs the cysteine residues must be maintained, and pg 113, lines 16-19, which demonstrates the mature ob only has cysteine at positions 117 and 167. Applicants' argument is not persuasive and unfounded. Amino acids 118-166 are not readily apparent from the teachings of amino acids of the disulfide loop are 117-167. Substituting any of amino acids 118-166 with cysteine is not readily apparent from cysteines at positions 117 and 167.

The substitutions in claim 167-168 remain new matter. Support cannot be found in any of the citations provided.

The substitutions in claim 169 remain new matter. Applicants point to the portions of the specification outlined for claims 166, 167, 168, 170, 171 and 173.

Applicants' argument is wholly unclear - the substitutions in the specification do not correlate to the substitutions in claim 169.

The substitutions in claim 170 a) remains new matter. Applicants point to the paragraph bridging pg 32-33 and pg 33, lines 11-14, which relate to positions 53, 98 and 92, not positions 52, 97 and 91 as claimed.

The substitutions in claim 171, a-g, remain new matter. Applicants point to the disclosure outlined for claim 166 in conjunction with that outlined for 170. Pg 34-35 taken with pg 32-33 do not correlate the substitutions in claim 171. Please explain each substitution (a-g) separately.

The substitutions in claim 172 remain new matter. No support for the substitutions can be found and the rejection has not been specifically addressed.

The substitutions in claim 173 remain new matter. Applicants point to pg 54, line 24, through pg 55, line 19, Fig. 22A-C and Fig 22A-B [sic]. The paragraph bridging pg 54-55 states:

In a specific embodiment, an ob fusion protein can be expressed. An ob fusion protein comprises at least a functionally active portion of a non-ob protein joined via a peptide bond to at least a functionally active portion of an ob polypeptide. The non-ob sequences can be amino- or carboxy-terminal to the ob sequences. More preferably, for stable expression of a proteolytically inactive ob fusion protein, the portion of the non-ob fusion protein is joined via a peptide bond to the amino terminus of the ob protein. A recombinant DNA molecule encoding such a fusion protein comprises a sequence encoding at least a functionally active portion of a non-ob protein joined in-frame to the ob coding sequence, and preferably encodes a cleavage site for a specific protease, e.g., thrombin or Factor Xa, preferably at the ob-non-ob juncture. In a specific embodiment, the fusion protein is expressed in Escherichia coli or in P. pastoris.

Fig. 22 is described as:

Alternative expression strategy in pichia. (A) Expression vector of an ob fusion with a His tag adopted from the pET expression system under control of the o~-mating factor signal sequence. (B) Schematic drawing of the structure of the recombinant ob fusion protein containing a His tag, which includes the or-mating factor signal sequence, putative KEX-2 and STE-13 cleavage sites, the His-tag, and a thrombin cleavage site, and which would yield ob with three surplus N-terminal amino acid residues.

The citations do not support substitutions at amino acids 52, 55, 70, 84...etc. as claimed. The citations do not describe the protein as having any N-terminal amino acid sequence selected from the group: methionine, SEQ ID NO: 38, 98, 26, 27, 28, 99 and 100, as claimed.

Written Description

Claims 124, 132-137, 139-143, 145-150, 155-159 and 163-174 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 124, 132-137, 139-143, 145-150, 155-159 and 163-174 lack written description because the specification does not adequately describe the "therapeutically effective amount" of a vector administered to a mammal "such that the mammal exhibits a decrease in body weight" or how to administer a vector to a mammal in vivo capable of "modifying the body weight of a mammal" as claimed. While it is readily apparent that the specification contemplates gene delivery, it is not readily apparent that applicants had overcome the unpredictability in the art and knew the specific conditions required to obtain therapeutic levels of ob expression *in vivo* using gene delivery. Pg 51, lines 16-25, discusses DNA operatively linked to expression control sequences. Pg 52, lines 9-17, discusses transforming a unicellular host and using a start codon. Pg 72, line 25, through pg 73, line 2, defines "therapeutically effective amount" i.e. an amount sufficient

to cause an improvement in a clinically significant condition in the host; however, the specific combination of vector, dose and route of administration required to reduce body weight using leptin gene therapy is not disclosed. For example, pg 83, line 4, is limited to introducing the ob gene into human fat cells. Therefore, it is not readily apparent that applicants were in possession or could reasonably have determined the combination of elements required to administer a vector in a "therapeutically effective amount such that the mammal exhibits a decrease in body weight" as claimed.

An adequate written description of a method of gene therapy requires more than a mere statement that delivery of a therapeutically effective amount of vector is part of the invention and reference to a list of possible routes of administration, vectors and promoters used in the method; what is required is a description of the specific combination of vector, promoter, and route of administration capable of having a decreasing body weight. It is not sufficient to define an amount solely by its principal biological property, i.e. a therapeutically effective amount because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of the combination of vector, promoter, route of administration and dosage required to decrease body weight. Also, naming a type of material generically known to exist, in the absence of knowledge as to what materials are capable of decreasing body weight, is not a description of that material. Thus, claiming all therapeutic effective amounts of a vector that decrease body weight without defining the specific combination of vector, promoter, route of administration and dosage required to do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has

arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific DNA sequences, which provide the means for practicing the invention.

Applicants argue the specification is not limited to delivering the OB gene to fat cells as described on pg 83, lines 18-19. Applicants argue the specification encompasses other delivery modalities. Applicants' argument is not persuasive. No other means of delivering the OB gene is taught in the specification. Intravenous administration of the leptin protein is discussed in the specification, but intravenous administration of the ob gene cannot reasonably be implied from the specification. The section of "nucleic acid-based therapeutic treatments" on pg 83-84 is limited to targeting fat cells and is separate and distinguished from protein based therapies discussed elsewhere in the specification. It is not readily apparent that applicants contemplated administering a leptin gene intravenously from the leptin protein therapy protocols because they are discussed distinctly and separately in the specification. Intravenous administration of the ob gene cannot reasonably be implied from the specification. The specification does not suggest performing gene therapy such that systemic expression of OB occurs, does not teach the cells that secrete OB and does not teach how to perform gene therapy such that OB is secreted systemically.

Applicants argue pg 72, line 5-9 and pg 72, line 25, through pg 73, line 5, provide written description for a "therapeutically effective amount." The citations disclose:

The polypeptides, nucleic acids, and antibodies of the invention have significant therapeutic potential. Preferably, a therapeutically effective amount of such an agent is administered in a pharmaceutically acceptable carrier, diluent, or excipient.
and

The phrase "therapeutically effective amount" is used herein to mean an amount sufficient to reduce by at least about 15 percent, preferably by at least 50 percent, more preferably by at least 90 percent, and most preferably prevent, a clinically significant deficit in the activity, function and response of the host. Alternatively,

a therapeutically effective amount is sufficient to cause an improvement in a clinically significant condition in the host. Administration of recombinant ob polypeptide results in weight loss, in particular, a decrease in fat tissue. Ob polypeptide can be prepared using standard bacterial and/or mammalian expression vectors, synthetically, or purified from plasma or serum, all as stated in detail earlier herein. Alternatively, increased expression of native ob polypeptide may be induce by homologous recombination techniques, as described supra.

The specification defines "therapeutically effective amount" but fails to provide adequately describe how much OB gene or vector encoding the OB gene meets applicants' definition.

Conclusion

No claim is allowed.

This is a continued examination of applicant's earlier Application No. 08/485943. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Patent Examiner